NTP Research Concept (Update): Selected Flame Retardants

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Nomination History and Status of Ongoing Studies
A series of flame retardants (FRs) was nominated for National Toxicology Program (NTP) testing by the Consumer Product Safety Commission (CPSC) in 2005, and approved by the NTP Board of Scientific Counselors for testing in 2006. Additional information about the nomination can be found on http://ntp.niehs.nih.gov/go/21158 and the 2006 Research Concept document is available at http://ntp.niehs.nih.gov/go/21099.

Due to a CPSC regulatory proceeding to reduce fires caused by ignition by small open flames and cigarettes, the use of FRs in upholstered furniture and bedding is expected to increase, thereby increasing the potential for consumer exposure. Upholstered furniture fires are a leading cause of residential fire deaths involving consumer products. The CPSC is considering the development of a performance standard to reduce the potential for ignition of upholstered furniture by cigarettes and small open flames, such as matches, cigarette lighters, and candles (CPSC 2008). Based on 1999-2002 data, the CPSC staff estimated 520 civilian deaths, 1040 injuries, and $242 million in property damage annually as a result of fires (Levenson 2005).

Compounds under this nomination included antimony trioxide (AO; CAS No. 1309-64-4), decabromodiphenyl oxide (DBDPO; CAS No. 1163-19-5; not included in the concept because of ongoing industry testing), tris(2-chloroisopropyl) phosphate (TCPP; CAS No. 13674-84-5), phosphonic acid, (3- {[hydroxymethyl]amino}-3-oxopropyl)- dimethyl ester (PA; CAS No. 20120-33-6), tris(hydroxymethyl) phosphine oxide (THPO; CAS No. 1067-12-5), and representative aromatic phosphates (APs), selected from tert-butylphenyl diphenyl phosphate (BPDP; CAS No. 56803-37-3), isodecyl diphenyl phosphate (IDDP; CAS No. 29761-21-5), isopropylated triphenyl phosphate (IPP; CAS No. 68937-41-7), 2-ethylhexyl diphenyl phosphate (EHDP; CAS No. 1241-94-7), triphenyl phosphate (TPP; CAS No. 115-86-6), and tricresyl phosphate (TCP; CAS No. 1330-78-5).

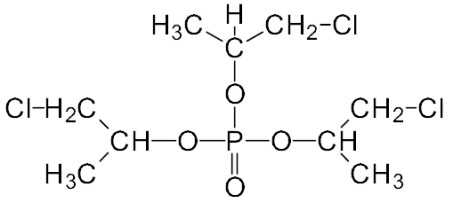
Testing of the chemicals under this project was proposed to proceed in three phases.

Phase 1
The first phase of the project included AO and TCPP. These compounds are currently on test by the NTP.

AO (Sb_2O_3)
AO is used in combination with flame retardants as a synergist. AO was nominated by CPSC and the National Institute of Environmental Health Sciences (NIEHS) for chronic oral, and inhalation and cardiotoxicity studies. Inhalation of particles was selected as the route for toxicology and carcinogenicity testing because of mixed results for the induction of lung tumors with three previous chronic inhalation studies, each with an

exposure duration of one year. Two-week inhalation studies in Wistar Han rats and B6C3F1 mice, which included standard toxicity endpoints and measurement of antimony in lung and blood, are complete. These studies were used to select exposure concentrations for the 2-year studies (currently on test). The two-year studies include a one year interim sacrifice to evaluate histopathology and genotoxicity, and measurements of antimony in lung and blood at various time points. The testing status of antimony trioxide can be found on: http://ntp.niehs.nih.gov/go/TS-10676-V.

TCPP



TCPP is a flame retardant that has been proposed as a substitute for polybrominated diphenyl ethers (PBDEs) and was nominated for subchronic and chronic testing by the oral route. The NTP study design team recommended subchronic toxicology, chronic toxicology and carcinogenicity studies in rats and mice, and a teratology study in rats. 90-day dosed-feed studies in Harlan Sprague Dawley rats (to include *in utero* and lactational exposure), and B6C3F1 mice are currently ongoing. These studies will be used to design later 2-year studies. A pilot study in time-mated pregnant rats is currently ongoing and will be used to select doses for a teratology study. The testing status of TCPP can be found on: http://ntp.niehs.nih.gov/go/TS-M20263.

Phase 2

The second phase of this project was designed to include studies on representative aromatic phosphates (APs), to be selected from BPDP, IDDP, IPP, EHDP, TPP, and TCP. The APs were nominated for subchronic and chronic (oral), neurotoxicity and/or developmental neurotoxicity testing.

The APs are high production volume compounds manufactured in the range of 1-50 million pounds per year, and hence were sponsored for data development under the EPA's High Production Volume Chemical (HPV) Challenge Program. It was determined that the NTP would address those toxicological data gaps identified in the CPSC nomination which are not covered in depth by industry voluntary testing activities.

Commercial AP products contain multiple isomeric forms and may also be formulated together with other flame retardants. Studies on these formulated products are difficult to interpret with respect to the toxicity of discrete AP components. In addition, there are data gaps which need to be addressed to more fully assess potential hazard of individual APs. Thus, the CPSC continues to be interested in the evaluation of this class of compounds by the NTP.

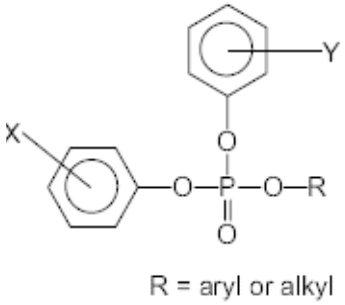
Phase 3

The third phase of the project was designed to include PA and THPO. Because these flame retardants covalently bind to treated fabrics, more information on extractability, especially the identity of migrating compounds, is needed prior to making any decisions regarding testing needs and study design. Thus, the NTP has deferred testing for these compounds due to difficulties in identifying appropriate test article(s).

The focus of the remainder of this document is to provide an update on the proposed studies for phase 2 (APs) of the project.

Research Concept Update: Aromatic Phosphate Flame Retardants

Background and Rationale



R = aryl or alkyl

	X	Y	R
Triphenyl phosphate (TPP)	-H	-H	-Ph
tert-Butylphenyl diphenyl phosphate (BPDP)	-H	-H	-t-BuPh
Tricresyl phosphate (TCP)	-Me	-Me	-MePh
2-Ethylhexyl diphenyl phosphate (EHDP)	-H	-H	-2-EtHx
Isodecyl diphenyl phosphate (IDDP)	-H	-H	-iDecyl
Isopropylated triphenyl phosphate (IPP)	-H or -iPr	-H or -iPr	-iPrPh

As the use of PBDEs in upholstered furniture and other consumer products is being phased out due to concerns about toxicity and environmental persistence, these agents are being replaced by new formulations that often include aromatic phosphates (APs) as flame retardants. In addition to use as FRs in polyurethane foams, these compounds are also used as plasticizers, hydraulic fluids, solvents, extraction agents, antifoam agents, and coatings for electronic devices.

The APs are released to the environment from industrial sources and during use and disposal of consumer products. Hence, humans can be exposed by a combination of oral, inhalation, and dermal routes; the most common sources being contaminated food and drinking water and house dust. Children may be at a higher risk of exposure since they are more likely to put FR treated materials in their mouths (ATSDR 2009). Due to increasing use of these compounds and insufficient toxicity information, the CPSC requested that the NTP conduct studies evaluating toxicity of these compounds to improve hazard characterization (detection of adverse effects and determining dose-response relationships) for use by CPSC in its regulatory role.

Within this class of compounds, the NTP has previously evaluated TCP, which was shown to cause reproductive toxicity and neurotoxicity, but was not carcinogenic (NTP 1994). Tri-*ortho*-cresyl phosphate (TOCP), an isomer of TCP, is an established neurotoxicant and reproductive toxicant, but was not present in the mixture studied by NTP (<0.1%). Due to structural similarity of this class of compounds with TCP, and high risk of exposure for children, studies to evaluate reproductive and developmental toxicity and neurotoxicity are warranted.

Key Issues

Commercially available flame retardants consist of a mixture of different isomers of APs, coupled with other non-AP components such as halogenated aryl and aliphatic esters. This poses difficulties in assessing the relative toxicity and hazard associated with the

individual test articles in the commercial mixture. There is limited information in the literature about the developmental and long-term effects of these compounds. Since these compounds are ubiquitously present in food, drinking water, and household dust, there is potential for exposure through multiple routes. Children may be more susceptible to toxic effects compared to adults due to both biological and behavioral (e.g. mouthing of flame retardant-treated materials) factors.

Proposed Approach

The overall goal of this research project is to investigate the potential for APs to cause systemic toxicity and carcinogenicity.

Specific Aims

1) Evaluation of the toxicity of aromatic phosphates as a class

Due to the numerous compounds in this class, short-term screening level studies are proposed to determine the general toxicity potential of the APs, and to obtain information on the influence of structural variations on toxicity. More specifically, the studies will be designed to evaluate the relative toxic effects of substituted phenyl rings and their metabolic products. These studies will also consider the toxicity of mixtures of the APs. *In vitro* high and medium throughput studies will be conducted to address mechanism of action and relative potency. Endpoints assessed will include neurotoxicity, steroidogenesis, liver enzymes and reproductive toxicity. Results from these studies may be used to evaluate the need for further in-depth testing of other compounds in this class.

2) Comprehensive evaluation of the toxicity of representative APs

Two representative compounds, TPP and BPDP, have been selected for initial in-depth testing and these studies will be conducted in parallel with the 'class studies' described above. These were selected based on high production volume (10-50 million pounds/year), ubiquitous presence in house dust, high environmental exposure, their anticipated increased use as replacement for some PBDEs, and lack of chronic toxicity and carcinogenicity data. Furthermore, the purpose of selecting these two compounds for initial testing was to assess comparative toxicity associated with presence versus absence of an alkyl substituted phenyl ring. This structural feature could potentially contribute to reproductive and neurotoxic effects by formation of a cyclic metabolic intermediate as seen previously with studies of TCP (NTP 1994). These studies will be conducted in 2 phases as follows:

Phase 1

This phase will include studies of developmental exposure in Harlan Sprague Dawley rats and of adult B6C3F1 mice and will be conducted in parallel.

a) Developmental exposure in Harlan Sprague Dawley rats

Dose range finding (DRF) studies will be conducted for TPP and BPDP on timed-pregnant Harlan Sprague Dawley (HSD) rats starting GD 6 with continuous exposure to the dams and/or pups through PND 21. The purpose of these studies is to obtain preliminary data to set a top dose for subsequent developmental toxicity studies, assess

maternal and fetal uptake and lactational transfer, and to develop methods for subsequent TK studies.

Doses from the DRF will then be used to design a developmental toxicity study with exposure starting on GD6 to include the utero/lactational period with continuous direct dosing to the pups until ~ PND 100. Toxicity endpoints will be assessed in the F1 and F2 generations. There will be separate cohorts for (i) neurotoxicity (ii) immunotoxicity (iii) teratology (iv) 90-day subchronic studies, and (v) breeding/littering. Complete pathological assessment will be performed. An additional ADME cohort may be included to characterize the *in vivo* absorption, disposition, and elimination of these compounds following administration of a single oral and intravenous dose if deemed necessary.

b) Sub-chronic studies in B6C3F1 mice

90-day subchronic studies in adult B6C3F1 mice will be conducted to evaluate the toxicity of TPP and BPDP using the oral route of exposure. The purpose of these studies is to provide information on the toxicity of these compounds in an additional species, and to set doses for a two-year carcinogenicity study in mice.

Phase 2

Two- year chronic toxicity and carcinogenicity studies

A two-year chronic toxicity study will be conducted with perinatal exposure in HSD rats and adult exposure in B6C3F1 mice on one or both compounds based on findings from the subchronic studies.

Significance and Expected Outcomes

Since some of the APs are being used as a replacement for PBDEs, there is an anticipated increase in their use and exposure. Since there is limited toxicity information on these compounds available in the literature, the CPSC has identified the need for additional studies to better inform the risk assessment of these agents. These studies will provide a comprehensive toxicity assessment of two ubiquitously present flame retardants, TPP and BPDP. This information will be useful for hazard and risk determinations for these chemicals. In addition, the *in vitro* and alternate animal studies will provide 'class' information on the mechanisms and relative potency of the other APs under this nomination. This information may subsequently be used by the NTP to assess other compounds in-depth in the future if deemed necessary.

References

ATSDR (2009) Toxicological Profile for Phosphate Ester Flame Retardants. *(Draft for Public Comment)* Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Babich, MA (2006) CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam. U.S. Consumer Product Safety Commission, Bethesda, MD.

Consumer Product Safety Commission (CPSC) (2008) Standard for the Flammability of Residential Upholstered Furniture; Proposed Rule. Federal Register, 73 (43): 11702-11752.

Levenson M (2005) Upholstered Furniture Addressable Fire Loss Estimates for 1999-2002. Directorate for Epidemiology. U.S. Consumer Product Safety Commission, Bethesda, MD.

National Toxicology Program (NTP) (1994) NTP Technical Report on the Toxicology and Carcinogenesis Studies of Tricresyl Phosphate (CASRN 1330-78-5) in F344/N Rats and B6C3F1 Mice (Gavage and Feed Studies). NTP TR 433. NIH Publication No. 94-3164. U.S. Department of Health and Human Services, Public Health Service.

U.S. EPA (2010) High Production Volume Information System (HPVIS)
Phenol, isopropylated, phosphate (3:1) (CAS No. 68937-41-7):
http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=25135566&epcount=26&epname=null&epdiscp=null&selchemid=100741&CategorySingle=Single
Phenol, tert-Bu derivs., phosphates (3:1) (CAS No. 220352-35-2):
http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=24947275&epcount=14&epname=null&epdiscp=null&selchemid=100039&CategorySingle=Single
Phosphoric acid, 2-ethylhexyl diphenyl ester (CAS No. 1241-94-7):
http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=25306409&epcount=29&epname=null&epdiscp=null&selchemid=101339&CategorySingle=Single
Phosphoric acid, isodecyl diphenyl ester (CAS No. 29761-21-5):
http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=24977669&epcount=18&epname=null&epdiscp=null&selchemid=101340&CategorySingle=Single
Phosphoric acid, tris(methylphenyl) ester (CAS No. 1330-78-5):
http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=25135753&epcount=35&epname=null&epdiscp=null&selchemid=100731&CategorySingle=Single